In the specification of the present application, the 7 cysteine region is mentioned on page 4, 2nd paragraph as well as on page 21, in the description of SEQ ID NO: 1. An article by Schlunegger & Grutter (1992) wherein the 3-D structure of TGF-p2 is described, e.g. on page 434: states "We therefore propose the general fold, including the TGF-β knot, of all the proteins of the TGF-β superfamily to be the same...". In addition, Daopin et al. (1992) describes the structure of TGF- β and comes to the same conclusion, which can be gathered from the last sentence of the abstract: "Sequence profile analysis of other members of the TGF-β superfamily, including the activin, inhibins, and several developmental factors, imply that they also adopt the TGF-β fold." Copies of the above discussed articles are attached to this response.

Since MP52 is a member of the TGF-β family, active fragments can be predicted. It is generally known that variations at the N-terminus of the mature protein of TGF-β-superfamily members are well tolerated (e.g. Sampath et al. 1992), which describes shortened mature forms of BMP- 7 (OP-1), which are also active.

In addition to the above discussed articles, several patent applications have been filed which show the positive influence of bone morphogenetic proteins on dentin. WO 96/26737 demonstrates the occurrence of corresponding effects. EP 0 665 739, shows the effect of bone morphogenetic proteins on periodontal tissue. This patent provides a summary of tests which shows the corresponding effects of bone growth factors.

Attached to the present response is an assay conducted by the scil Biomedicals company (Title: Enhancement of bone growth by coating of osteoconductive beta- TCP with recombinant human growth/differentiation factor-5 (rhGDF-5), Authors: Poehling et al.) as well as two articles, Spiro et al. (Biochemical Society Transactions (2000), Vol. 28, part 4) and

Nishitoh. Nishitoh shows that it was already known before the priority date of the present application that MP52 uses type I and II receptors, i.e. that it follows the same signaling mechanism as other TGF-β family members. Nishitoh teaches that GDF-5/MP52 preferably binds to Alk-6/BMPR-IB in the presence of different receptors of type II.

The office action indicates that the present invention does not disclose, which dimer of the TGF-β family can be combined with MP52. Applicants respectfully point out that page 3 of the present specification indicates that many members of the TGF-β superfamily show a cartilage and/or bone-inducing potential. In view of this disclosure, one skilled in the art could easily determine which of the proteins of the TGF-β superfamily can be used in combination with MP52. In addition, Nishitoh states on pages 21350 and 21351 that "Taken together, the binding profile of GDF-5 in non-transfected cells is different from that of BMP-2, BMP-4, or OP-1/BMP-7; i.e. GDF-5 preferentially binds to BMPR-IB but not to ActR-1 and BMPR-IA". Thus, Nishitoh shows that there are slight differences in binding compared to other bone-inducing BMPs. One skilled in the art would know that a useful supplementation is possible, if both proteins induce bones and if at least partially different receptor ways are involved, which are both successful.

The attached Spiro et al. article shows two assays which were carried out with primates, the "Primate long-bone- defect-model" and the "Primate spinal-fusion model". The first test is similar to the test described in the attached Declaration. A defect is established (1 .5 cm) and the defective bone is splinted so that the bones remain in the right position for growing together. With the help of GDF-5 (MP52), the defect can completely be removed. This application could be used when dealing with bone fractures and bone defects. The latter model shows that vertebrae can successfully be linked together with GDF-5/MP52 and thus movable bone parts can be immobilized.

The attached scil Biomedicals paper (Poehling) shows that beta- TCP forms significantly more bone with MP52 than beta- TCP alone. The link to dental and maxillofacial areas is in the introduction. There, it is stated that until now "Autogenous bone has been considered the 'gold standard' graft material for reconstruction of defects in the dental and maxillofacial area". Autogenous bone grafts showed disadvantages so alternative materials were evaluated. scil Biomedicals is now developing the material TCP with GDF-5 (MP52), which indicates that GDF-5 in combination with TCP can be advantageously used in the dental and maxillofacial area.

Claims 25-28 were objected to due to the plural use of the language "and/or". As suggested by the Examiner, claims 25 and 28 have been amended to recite "and/or" only once. In view of these amendment, applicants request that this objection be withdrawn.

Applicants respectfully submit that all of claims17-25, 27-28 and 30 are enabled by the present specification and the knowledge in the art and are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below to set up an interview to advance prosecution.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

RESPECTFULLY SUBMITTED,					
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Enclosures: Marked up copy of claims
Unsigned Declaration
Scil (Poehling) paper
Spiro article
Nishitoh article
Schlunegger article
Daopin article
Sampath article

Appendix 1

Marked up copy of claims to show amendments

21. (Twice Amended) A process for the production of an implant material according to claim 28, the process comprising applying the MP52 protein ~~or DNA encoding such MP52 protein~~ in and/or on the calcium phosphate matrix as a solution in a solvent such that a homogeneous distribution of the MP52 protein ~~or DNA encoding such MP52 protein~~ in and/or on the calcium phosphate matrix is achieved.

23. (Twice Amended) The process of claim 21, wherein the MP52 protein ~~or DNA encoding such MP52 protein~~ is concentrated by in situ precipitation from the solvent in the calcium phosphate matrix by admixing a precipitating solvent.

25. (Twice Amended) A method of treating a disease which affects cartilage ~~and/or bone~~, bone, or cartilage and bone and/or damage to cartilage ~~and/or bone~~ ~~bone~~, bone, or cartilage and bone in a patient in need thereof, the method comprising implanting an implant material according to claim 28, into the patient.

28. (Twice Amended) An implant material suitable for cartilage ~~and/or bone~~, bone, or cartilage and bone growth comprising a matrix material which is composed of a crystallographically phase-pure calcium phosphate and applied in and/or on said matrix a cartilage inducing, bone inducing, or cartilage and bone ~~and/or bone~~ inducing MP52 protein ~~or a DNA encoding such MP52 protein~~, wherein the MP52 protein is selected from the group consisting of

(a) a protein comprising amino acid 1 to 501, 28 to 501, 361-400 to 501, 381 to 501, 382 to 501, 400 to 500 of SEQ ID NO. 1,

(b) a protein according to (a) which is a homodimer, and

(c) a protein according to (b) in combination with a dimer of another protein of the TGF-β superfamily which shows cartilage or bone-inducing potential.